IMPROVEMENT OF PHYSICOCHEMICAL PROPERTIES OF DRUGS – A PARTICLE ENGINEERING APPROACH

A synopsis submitted for the registration to degree of
Doctor of philosophy
(Pharmaceutical Sciences)

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2020

Research Proposal

(Synopsis)

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PART I –INTRODUCTION

1. Importance of Research Topic

The most preferred route of administration is oral route across the Pharmaceutical dosage forms due to its ease of administration, acceptability, Stability of formulation and ease of handling. Despite of development of many innovative drug formulations tablet are still most accepted by the patients which accounts for at least 50% of all oral drug delivery system and 70 % of the all pharmaceutical preparations.[1]

The ultimate goal of product development is to consistently deliver the intended dose of a drug in a bioavailable, safe and efficacious manner. One of the key components in rational formulation and process design is to acquire and utilize knowledge of drug properties to facilitate the application of various basic and applied sciences such as pharmaceutical science, various branches of chemistry, biological sciences, engineering principles and statistics in the product development process.[2]

The physical properties of the powders are most important factor in the pharmaceutical industry. The knowledge of the flow properties of powder is of great importance in pharmaceutical processes such as blending, tablet compression, capsule filling, and transportation and in scale up operations[3]. Powder flow properties are measured using a number of parameters such as angle of repose, compressibility index (Carr's index) and Housner ratio. The powder flow is a key factor in the series of processes involved in the manufacturing of pharmaceuticals, Good flow properties help to achieve acceptable content uniformity, weight variation and physical consistency.[4]

The conventional methods of improvement of flow properties of the Active Pharmaceutical ingredients and excipients in order to make the Tablet or Capsule dosage form are Wet Granulation, Dry granulation, Fluidized Bed Granulation, Melt Granulation and Direct Compression.[5]

The direct tableting technique has been extensively investigated and successfully industrialized for some drugs due to requirements of fever machines and operation steps. Present progresses in direct tableting is accomplished by the addition of large quantity of fillers to the drug powder to improve various micromeritic properties. Direct tableting necessitates an active ingredient powder that excels in flowability, bendability and mechanical strength. Currently limited tablets are on commercial production that can be made by direct tableting and development of active pharmaceutical agglomerates that can be directly compressible and forms tablets are being waited. Most powders cannot be compressed directly in to tablet because of the lack of the proper characteristics of binding or bonding together in to compact entity. For these reason, particle design is done to improve the properties of particles to impart a new function to preparation and to guarantee more stable and reliable powder processing. Thus the efficiency of the tablet manufacturing can be improved by using directly compressible materials instead of having conventional methods of particle modifications.[6]

Spherical crystallization is particle engineering technique, by which crystallization and agglomeration can be carried out in one step and which has been successfully utilized for improvement of flowability, compatibility, solubility and bioavailability of drugs. Spherical crystallization technique of particle design of drugs has emerged as one of the areas of interest in pharmaceutical manufacturing and recently came into the forefront of interest or gained great attention and importance due to the fact that crystal habit (form, surface, and size and particle size distribution) can be modified during the crystallization process. General methods of spherical crystallization are spherical agglomeration, emulsion solvent diffusion and ammonia diffusion method.[7]

2. Hypothesis of Research Topic

The present investigation is based on hypothesis that improvement of physicochemical properties of the active pharmaceutical ingredients such as Particle size, Flowability, packability, compressibility and solubility of the active pharmaceutical ingredients belonging to BCS Class-II drugs through particle engineering.

3. Scientific and Practical Values of the research topic

Advancements in particle engineering in pharmaceutical industry allows to modify crystal habit of the drugs which leads to the improvement of mechanical, physical and chemical properties of pharmaceutical product. The strategies for improving and maximizing the flow properties include spray drying, spherical crystallization, crystallo-co- agglomeration etc.

Particle engineering technique is an area of interest by which we can handle the problems related to pharmaceutical manufacturing issues of active pharmaceutical ingredients having poor flow properties by improving physiochemical properties viz. Particle size, Flowability, packability and compressibility, Solubility etc.

4. Research Objectives

- Selection of potential drug candidate based on physicochemical properties.
- Analytical suitability, method development and validation for selected drugs candidate specified as per International Conference on Harmonization guidelines (ICH Q2 R1).[8]
- Selection of methodology based on physicochemical attributes of selected drug candidate and feasibility.
- Evaluation of particle engineered molecule *viz*. particle size, particle size distribution, particle morphology, flow properties etc.
- Assortment of promising engineered form and further its development for formulation and development.
- Selection of critical attributes and formulation optimization with experimental design.
- Evaluation of optimized formulation.
- Stability study of optimized particle engineered candidate and its dosage form.

PART II –LITRATURE REVIEW

- ***Kawashima Y. et al[9]., 2003.*** Spherical crystallization of ascorbic acid was prepared by two different mechanisms, i.e. Emulsion Solvent Diffusion (ESD) and Spherical Agglomeration (SA). The micromeritic properties of agglomerated crystals, such as flowability, packability and compactability were dramatically improved, resulting in successful direct tableting without capping under a practical compression speed. Remarkable fragmentation, increased plastic deformation and lowered elastic recovery of the agglomerated crystals during tableting process were responsible for improving the compactability of the Ascorbic Acid agglomerated crystals.
- ***Hongbo Chen, Changquan Calvin Sun, et al[10]., 2018,*** Spherical crystallization by the quasi-emulsion solvent diffusion method was used to engineer a poorly flowing model compound, ferulic acid (FA), to attain superior mechanical properties, particle size distribution, and morphology. The engineered FA particles enabled the successful development of DC tablets containing 99% FA, which is in sharp contrast to the maximum 10% FA loading using as-received FA. The record high active pharmaceutical ingredient loading in this work illustrates the potential for spherical crystallization to enable high drug loading when developing a tablet product using the DC manufacturing process.
- ***Paradkar A. R. et al[11]., 2002,*** carried out spherical crystallization of celecoxib by solvent change method in which acetone as a good solvent and water used as a bad solvent and Dichloromethane as a bridging liquid. To impart strength and sphericity to the agglomerates Hydroxypropyl methylcellulose (HPMC) was used and effect of amount of bridging liquid and speed of agitation was studied by application of QbD approach. The effect of variables on micromeritic, mechanical, compressional and dissolution behavior was evaluated by QbD approach. To evaluate the properties of agglomerates IR spectroscopy, powder X-ray diffraction and differential scanning calorimetry was carried out. From the results it was clear that Particle size, bulk density and drug release were found to be significantly affected by the variables.

- ***Smiti Kumar et al[12]., 2008,*** Spherical crystallization of Mebendazole was carried out by using Spherical Agglomeration method using different polymers such as polyethylene glycol, cross-povidone, starch, cross carmellose sodium, hydroxyl propyl methyl cellulose (HPMC), hydroxyl propyl cellulose (HPC), ethyl cellulose (EC), Eudragit®S100, Eudragit®RLPO, Eudragit®RD100, Eudragit®E and bridging liquids such as hexane, octanol, toluene, dichloromethane. The effect of various parameters like polymer type, polymer concentration and stirring rate was studied to optimize the final conditions for spherical crystallization. Amongst all the polymers the best spherical crystals with an aspect ratio of 1 were seen in the presence of Eudragit®S100 at stirring speed of 500 rpm. Agglomerates generated using HPC and HPMC also showed significant improvement in AR from a value of 12 for pure Mebendazole to 1–2 for these processed crystals, signifying better flow and compressibility. These agglomerates also showed improved dissolution compared to Mebendazole, however the crystals from Eudragit® had a poor drug release because of its pH dependent release property, which failed to release in acidic medium. Such a technique can successfully be employed to generate ready-to-formulate API, thus saving on time and effort at the formulator's end.
- ***Pritish Kurumkar et al[13]., 2008,*** crystallo-co-agglomeration technique is extension of the spherical crystallization technique which enables simultaneous crystallization and agglomeration of 2 or more drugs or excipients. By using crystallo-co-agglomeration technique prepared directly compressible agglomerates of aceclofenac-paracetamol Acetone-water system containing PEG 6000, PVA and HPMC K100M was used in crystallization system. Acetone acted as a good solvent for Aceclofenac and bridging liquid for agglomeration. Aceclofenac was crystallized from acetone and agglomerated with Paracetamol. The agglomerates were evaluated for micromeritic properties, mechanical properties, moisture content, compressibility, packability and in vitro dissolution study. Whereas micromeritic property reveals that the agglomerates exhibit very good flow property with very good compactability and with low friability. In vitro dissolution study revealed that varying in level the polymer concentration prolongs the drug release. It has been concluded that crystallo-co-agglomeration technique is a

suitable alternative method to the granulation process and can be used for design of sustained release Aceclofenac-Paracetamol agglomerates.

- ***Maryam Maghsoodi et al[14].2008***, Crystallo-co-agglomeration technique used to obtain directly compressible agglomerates of naproxen containing disintegrant Acetone–water containing hydroxypropylcellulose (HPC) was used as the crystallization medium. Acetone acted as a good solvent for naproxen as well as a bridging liquid for agglomeration of crystallized drug with disintegrant and aqueous phase as non-solvent. The agglomerate exhibits good flow and packing properties. The improved compaction properties of the agglomerated crystals were due to the fragmentation which occurred during compression. It has shown that disintegrant did not undergo structural modifications. The dissolution rate of naproxen from the agglomerates could be controlled by the amount of included disintegrant, Disintegrant was included both intra-granularly and extra-granularly during agglomeration of naproxen particles, tablets containing these agglomerates dissolved at a faster rate than the tablets containing crystallized naproxen with the same amount of disintegrant incorporated only extra-granularly by physical mixing. In conclusion, the properties of agglomerated crystals, such as flowability, compatibility and dissolution rate was improved profoundly using the developed technique resulting in successful direct tableting without need to additional process of physical blending of agglomerates and disintegrants.
- ***Vinod L Gaikwad et al[15], 2019,*** prepared spherical agglomerates by using Crystallo-co-agglomeration technique. He was used simple beaker and laboratory stirrer to prepare agglomerates, talc was used as a main ingredient with Indapamide and Hydroxy propyl methyl cellulose 15 cps and polyethylene glycol 6000 was used to impart desired sphearicity, strength, and deformability to the agglomerates and Ethyl cellulose 10 cps was used to improve the strength of agglomerates and to achieve extended release profile. The effect of type and quantity of polymer on the formation of agglomerates was evaluated. And other micromeritic properties was evaluated and was found good yield with better flow properties and tablets with lesser friability was obtained. Dissolution studies were carried out and dissolution was extended up to 6 hrs which was due to the formation of the miniscular dosage

form and hydrophobicity incorporated due to talc and was concluded that Crystallo-co-agglomeration technique could be successfully used for the preparation of directly compressible high strength extended release spherical agglomerates.

- ***Yadav A. V. et al[16]., 2008,*** Prepared polymeric carbamazepine spherical crystals by emulsion solvent diffusion technique, with improved solubility, dissolution rate, and physicochemical properties by ethanol-chloroform-water as the solvent system, In the recrystallization process the hydrophilic polymers like polyethylene glycol, chitosan and hydrophobic polymer like Eudragit RSPO were used. The prepared Carbamazepine crystal were characterized against Carbamazepine as such in term of morphology, X-ray diffraction, FTIR, drug content, solubility, dissolution rate crushing strength, wettability, flowability, and packability and found improved significantly. The research finding was that spherical crystal with polyethylene glycol and chitosan showed higher crushing strength when compared with the hydrophobic polymer (Eudragit RSPO).
- ***Janki Fadke et al[17].,2015,*** Spherical crystallization was prepared to achieve better solubility and bioavailability and better processability to prepare tablets with direct compression method. Spherical crystal agglomerates of itraconazole prepared by quasi emulsification solvent diffusion method using Soluplus and polyethylene glycol 4000 (PEG 4000) and which showed increased solubility that is 540 µg/ml as compared to 12 µg/ml. Significantly improved micromeritic properties compared to the plain drug suggested its suitability for direct compression. The antifungal activity of itraconazole was retained in the SCA form as evidenced from the results of the disc diffusion method. The tablets manufactured showed better hardness and lesser disintegration time. The in vitro dissolution studies showed significant difference in the dissolution profiles of pure drug (21%) and SCA formulation (85%) which was even greater than that of marketed preparation (75%). In vivo pharmacokinetic showed significant enhancement in Cmax and AUC0−t with relative bioavailability of 225%. The SCA formulation seems to be promising for enhancement of oral bioavailability of itraconazole.
- ***Amit R. Tapas et. el[18]., 2010,*** Spherical agglomerates of Valsartan was prepared to improve solubility, Dissolution and micromeritic properties. Spherical

agglomeration prepared by using quasi emulsion solvent diffusion method using methanol - water - dichloromethane as a good solvent - poor solvent - bridging liquid. The hydrophilic polymers like polyvinyl pyrrolidone, Hydroxypropyl β-cyclodextrin, Hydroxypropyl methylcellulose were used in agglomeration process. Then spherical agglomerates was characterized by differential scanning calorimetry (DSC), X-ray diffraction (XRD), IR spectroscopic studies and scanning electron microscopy (SEM) and micromeritic properties. It was found that valsartan agglomerates shows improved solubility and dissolution rate in addition to improving the micromeritic properties.

- ***Ozyazici M. et al[19], 2012,*** Mefenamic Acid spherical agglomerates prepared by solvent crystallization method using Ethanol-Dichloromethane as solvent. Different acrylic polymers used such as Eudragit@ RS 100, Eudragit@ RL 100 and Eudragit@ L 100 and combination sof acrylic polymers in different ratio. The influence of various formulation factors on the encapsulation efficiency, as in vitro drug release, and micromeritic properties was investigated. It was found that optimized agglomerates observed improvement of dissolution rate and sustained release delivery of poorly water-soluble drug in one step.
- ***Gadade D. D. et all20,2017,*** Lornoxicam co-crystals were prepared by using nineteen different conformers such as benzoic acid, salisylic acid, malonic acid, 4-hydroxy benzoic acid, succinic acid, tartaric acid, fumaric acid, ascorbic acid, saccharin sodium etc. Cocrystals were prepared by neat grinding method. The prepared cocrystals were evaluated for solubility, powder characteristics, assay and in vitro dissolution study. The solid-state property was characterized by differential scanning calorimetry, Fourier transform infrared spectroscopy, powder X-ray diffraction analysis and Raman spectroscopy. Maximum solubility and dissolution rate were observed with cocrystal prepared using saccharin sodium. Co-crystallization leads to increased solubility and improved in vitro dissolution of Lornoxicam.

PART III- RESEARCH WORK PLAN

Phase-I	1. Extensive Literature Search	**6 Months**
Phase-II	1. Procurement and Physicochemical studies of drugs (API's) and other raw materials. 2. Analytical method development (U.V. and/or HPLC) and validation for drug candidate.	**6 Months**
Phase-III	1. Selection of feasible approaches for improvement of processability of selected drugs candidate. 2. Preparation and Evaluation of particle engineered active pharmaceutical ingredients. 3. Optimization of formulation variables for desired responses.	**6 Months**
Phase-IV	1. Characterization of particle engineered formulations. 2. Formulation optimization by particle engineered Active Pharmaceutical Ingredients.	**6 Months**
Phase- V	1. Evaluation of formulation prepared by particle engineered Active pharmaceutical ingredients. 2. Stability study of formulation and Particle engineered Active pharmaceutical Ingredients.	**6 Months**
Phase-VI	1. Compilation of Data 2. Research Communication 3. Report Writing and submission of thesis	**6 Months**
***Chapter scheme may be altered in view of dictates of experiment.**		

PART IV- EXPECTED RESULTS AND OUTCOME

The present investigation of particle engineering approach is expected to result in improved physicochemical characteristics of Active Pharmaceutical Ingredients. This may dramatically improve the processability of such drugs. Particle engineered form of Active Pharmaceutical Ingredients may be convincingly improved Particle size, Flowability, packability and compressibility etc. The pharmaceutical performance of Active Pharmaceutical Ingredients may be radically explored through this research investigation.

Further it shall improve the solubility of Active Pharmaceutical Ingredients and/or improvement in Dissolution characteristics of Pharmaceutical Product manufactured by particle engineered Active Pharmaceutical Ingredients to perk up industrial applicability of the proposed research investigation. The present investigation has inherent prospective in terms of development of intellectual property rights (IPR). It may lead to IPR in terms of publications and patent(s).

References:

1. Nachajski N. J, Bazela A., Zarzycka M., Broszczyk A, Kołba Aand,. Kołodziejczyk M.K., Effect of API on Powder Flowability, Direct Compression and Properties of Orally Disintegrating Tablets: A Preformulation Study, Indian J Pharm Sci, 2019; 81(3) :489-495.
2. Deliang Zhou and Yihong Qiu, Understanding Drug Properties in Formulation and Process Design of Solid Oral Products, Journal of Validation Technology [Autumn 2010].
3. Arindam Chatterjee, Madan Mohan Gupta, Birendra Srivastava, Spherical rystallization: A technique use to reform solubility and flow property of active pharmaceutical ingredients, International Journal of Pharmaceutical Investigation, 2017;7:4-9.
4. Sarath Chandran C, 2Theju John Thomas,Vipin K V, Amitha S, Crystallo-Co-Agglomeration: An Effective Tool to Change the Powder Characteristics of Indomethacin IP, International journal of pharmacy and Pharmaceutical Research, November 2016 Vol.:7, Issue:4.
5. Srinivasan Shanmugam, Granulation techniques and technologies: recent progresses, BioImpacts, 2015, 5(1), 55-63.
6. Yadav A.V. and Yadav V. B., Designing of pharmaceuticals to improve physicochemical properties by spherical crystallization technique, Journal of Pharmacy Research, Vol.1.Issue 2. Oct-December 2008.
7. Ghodake P P, Bhosale R R, Osmani R A, Harkare B R, Shaikh S M, Spherical Crystallization: A Distinctive Practice in Pharmaceutical Processing, International Journal for Pharmaceutical Research Scholars (IJPRS), V-2, I-4, 2013.
8. Ich Harmonised Tripartite Guideline, Validation Of Analytical Procedures: Text And Methodology Q2(R1),
9. Kawashima Y, Imai M., Takeuchi H., Yamamoto H., Kamiya K., Hino T., Improved flowability and compactibility of spherically agglomerated crystals of ascorbic acid for direct tableting designed by spherical crystallization process, Powder Technology 130 (2003) 283– 289.
10. Hongbo Chen , Aktham Aburub, Changquan Calvin Sun, Direct Compression Tablet Containing 99% Active Ingredient - A Tale of Spherical Crystallization, Journal of Pharmaceutical Sciences xxx (2018) 1-5.
11. Paradkar A. R., A. P. Pawar,J. K. Chordiya,V. B. Patil &A. R. Ketkar, Spherical Crystallization of Celecoxib, Pages 1213-1220 | Published online: 29 Oct 2002.
12. Smiti Kumar, Garima Chawla, and Arvind K. Bansal, Spherical Crystallization of Mebendazole to Improve Processability, Pharmaceutical Development and Technology, 13:559–568, 2008.
13. Pritish Kurumkar, Sunil Dewani, Inayat Bashir Pathana Harsha Sonaye, Preparation Of Spherical Crystal Agglomerates Via Crystallo-Co-Agglomeration Technique, Digest Journal of Nanomaterials and Biostructures Vol. 7, No. 3, July - September 2012, p. 1223 – 1236

14. Maryam Maghsoodi, How spherical crystallization improves direct tableting properties: a review, Advanced Pharmaceutical Bulletin, 2012, 2(2), 253-257.
15. Vinod L. Gaikwad, Namdeo R. Jadhav, Atmaram P. Pawar & Kakasaheb R. Mahadik, Development of High-Strength Extended-Release Multiparticulate System by Crystallo-co-agglomeration Technique with Integration of Central Composite Design, AAPS PharmSciTech volume 20, Article number: 192 (2019).
16. Adhikrao Yadav and Venkat Yadav, Preparation and evaluation of polymeric carbamazepin spherical crystals by emulsion solvent diffusion technique, Asian Journal of Pharmaceutics(Vol. 3, Issue 1).
17. Janki Fadke, Jagruti Desai, and Hetal Thakkar, Formulation Development of Spherical Crystal Agglomerates of Itraconazole for Preparation of Directly Compressible Tablets with Enhanced Bioavailability, AAPS PharmSciTech (# 2015).
18. Amit R. Tapas, Pravin S. Kawtikwar, Dinesh M. Sakarkar, Spherically agglomerated solid dispersions of valsartan to improve solubility, dissolution rate and micromeritic properties, International Journal of Drug Delivery 2 (2010) 304-313.
19. Mine Ozyazici, Ferhan Sevgi, Cetin Pekcetin, Buket Sarpas, and Safak Sayin, Sustained release spherical agglomerates of polymethacrylates containing mefenamic acid: in vitro release, micromeritic properties and histological studies, Pharmaceutical Development and Technology, 2012; 17(4): 483–493.
20. Gadade D.D.,Kulkarni D. A,Rathi P.B., Pekamwar S. S. And Joshi S. S., Solubility Enhancement of Lornoxicam by Crystal Engineering, Indian J Pharm Sci 2017;79(2):277-286.

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